

beta-Arrestin2 mediates the initiation and progression of myeloid leukemia.

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Authors: M Fereshteh, T Ito, J J Kovacs, C Zhao, H Y Kwon, V Tornini, T Konuma, M Chen, R J Lefkowitz, T Reya

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Public Summary:

β -Arrestins were initially discovered as negative regulators of G protein-coupled receptor signaling. Although β -arrestins have more recently been implicated as scaffold proteins that interact with various mitogenic and developmental signals, the genetic role of β -arrestins in driving oncogenesis is not known. Here we have investigated the role of β -arrestin in hematologic malignancies and have found that although both β -arrestin1 and -2 are expressed in the hematopoietic system, loss of β -arrestin2 preferentially leads to a severe impairment in the establishment and propagation of the chronic and blast crisis phases of chronic myelogenous leukemia (CML). These defects are linked to a reduced frequency, as well as defective self-renewal capacity of the cancer stem-cell population, in mouse models and in human CML patient samples. At a molecular level, the loss of β -arrestin2 leads to a significant inhibition of β -catenin stabilization, and ectopic activation of Wnt signaling reverses the defects observed in the β -arrestin2 mutant cells. These data cumulatively show that β -arrestin2 is essential for CML disease propagation and indicate that β -arrestins and the Wnt/ β -catenin pathway lie in a signaling hierarchy in the context of CML cancer stem cell maintenance.

Scientific Abstract:

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